onal Cancer Institute
RCINOGENESIS
Technical Report Series
No. 4
January, 1977

BIOASSAY OF DIMETHOATE FOR POSSIBLE CARCINOGENICITY

CAS No. 60-51-5

NCI-CG-TR-4

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
National Institutes of Health

BIOASSAY OF DIMETHOATE

FOR POSSIBLE CARCINOGENICITY

Carcinogen Bioassay and Program Resources Branch
Carcinogenesis Program
Division of Cancer Cause and Prevention
National Cancer Institute
Bethesda, Maryland

November 1976

DHEW Publication No. (NIH) 77-804

BIOASSAY OF DIMETHOATE
FOR POSSIBLE CARCINOGENICITY

Carcinogenesis Program, Division of Cancer Cause and Prevention

National Cancer Institute

November 1976

CONTRIBUTORS: This report presents the results of the carcinogenesis bioassay conducted by the Carcinogen Bioassay and Program Resources Branch, Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute (NCI), Bethesda, Maryland. This research was conducted at Gulf South Research Institute, New Iberia, Louisiana, initially under direct contract to the NCI and currently under a subcontract to Tracor Jitco, Inc., the prime contractor for the NCI Carcinogenesis Bioassay Program.

This report was prepared at NCI by Dr. J. F. Douglas[1] and reviewed by Dr. C. Cueto[1]. It was subsequently reviewed by the toxicologists, Drs. W. E. MacDonald[2] and J. F. Robens[2], and the final report was compiled and edited at Tracor Jitco by Dr. E. W. Gunberg[2].

The experimental design was determined by Drs. J. H. Weisburger[1,4] and R. R. Bates[1]; the dose levels were selected by Drs. T. E. Shellenburger[3,5], J. H. Weisburger, and R. R. Bates; animal treatment and observations were supervised by Drs. T. E. Shellenburger and H. P. Burchfield[3] with the technical assistance of Ms. D. H. Monceaux[3] and Mr. D. Broussard[3]; Dr. W. E. Greer[3] was the veterinarian in charge; and Drs. E. Bernal[3] and B. Buratto supervised the necropsies. The histopathologic evaluation was conducted at Experimental Pathology Laboratories, Herndon, Virginia, by Drs. R. A. Renne[6,7], J. F. Ferrell[6], and C. E. Gilmore[6] and the diagnoses included in this report represent the interpretation of these pathologists. Pathologists at NCI

and Dr. C. N. Barron[2] have reviewed selected slides and concur with the overall pathologic evaluation of the study.

Compilation of individual animal survival, pathology, and summary tables was performed by EG&G Mason Research Institute[8]; statistical analyses were performed by Dr. K. C. Chu[1], using methods selected for the Bioassay Program by Dr. J. J. Gart[9]. This report was reviewed by members of the participating organizations[1,2,3,6].

---

[1]Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

[2]Tracor Jitco, Inc., 1776 E. Jefferson Street, Rockville, Maryland.

[3]Gulf South Research Institute, Atchafalaya Basin Laboratories, P.O. Box 1177, New Iberia, Louisiana.

[4]Now with the Naylor Dana Institute for Disease Prevention, American Health Foundation, Hammond House Road, Valhalla, New York.

[5]Now with the National Center for Toxicological Research, Jefferson, Arkansas.

[6]Experimental Pathology Laboratories (EPL), 17 Pine Street, Herndon, Virginia.

[7]Now with Battelle Pacific Northwest Laboratories, Battelle Boulevard, Richland, Washington.

[8]EG&G Mason Research Institute, 1530 East Jefferson Street, Rockville, Maryland.

[9]Field Studies and Statistics, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

SUMMARY

A bioassay of the carcinogenicity of technical-grade dimethoate was conducted using Osborne-Mendel rats and B6C3F1 mice. The test material was administered in feed to groups of 50 rats of each sex at either of two concentrations for 80 weeks, followed by 35 weeks of observation. Initial doses were not well tolerated; therefore, they were reduced during the study. The "time-weighted average doses" for rats were 155 and 310 ppm for males and 192 and 384 ppm for females. All surviving rats were killed between 113 and 115 weeks.

Dimethoate was administered in feed to groups of 50 male and 50 female mice at two concentrations. Female mice received diets containing 250 and 500 ppm of dimethoate for 80 weeks; male mice received the same dosage. However, high-dose males were returned to the control diet at 60 weeks, and low-dose males at 69 weeks. All surviving mice were killed between 93 and 94 weeks.

Tremors and hyperexcitability, both indications of dimethoate toxicity, were observed in the treated animals. However, it is considered that the low-dose group of rats and both dose groups of mice survived long enough to permit an evaluation of carcinogenicity. Pathologic evaluation revealed no statistically significant increase in tumors associated with dimethoate treatment in either species of animal, and it is concluded that there was no carcinogenic effect under the conditions of the experiment.

TABLE OF CONTENTS

APPENDICES

TABLES

FIGURES

I. INTRODUCTION

Dimethoate is the common name for the organophosphorous insecticide, O,O-dimethyl-S-(N-methylcarbamoylmethyl)phosphorodithioate. This compound, which has been in use since 1956 as an insecticide and acaricide, is registered for insect and mite control on agricultural crops and ornamental plants (Federal Register, 1975). It is also registered as a residual fly spray in animal quarters (Chemical Economics Handbook, 1969).

Dimethoate was tested as part of the carcinogenesis bioassay because it is a widely used organophosphorous pesticide. Recent research on Wistar rats and AB strain mice by Gibel et al., (1973) suggests that dimethoate may have carcinogenic properties.

II. MATERIALS AND METHODS

A. Chemical

Technical-grade dimethoate (CYGON®), generally 94-96% pure (Martin, 1971), was purchased from American Cyanamid, Princeton, New Jersey, in one batch for use in the chronic study. The batch was analyzed at Gulf South Research Institute by melting point, infrared, ultraviolet and mass spectroscopy, nuclear magnetic resonance spectrometry, thin-layer chromatography, and gas-liquid chromatography which showed the purity of the batch to be 90-100%. This technical-grade batch was spectroscopically and chromatographically similar to analytical-grade dimethoate (99.3% pure). No attempt was made to identify impurities.

B. Dietary Preparation

All diets were formulated using Wayne® Lab Blox Meal (Allied Mills, Inc., Chicago, Ill.) to which was added the required amount of dimethoate for each dietary concentration. The test compound was first dissolved in a small amount of acetone (Mallinckrodt Chemical Works, St. Louis, Mo.), which was then added to the feed. Corn oil equal to 2% of the final feed weight was then added, primarily as a dust suppressant. The diets were mechanically mixed to assure homogeneity and to allow for

evaporation of the acetone. The corn oil (Louana®) was produced by Opelousas Refinery Co., Opelousas, Louisiana. The prepared diets were analyzed regularly throughout the test to assure uniformity. Water and the formulated diets were made available ad libitum to the experimental animals and were replaced three times per week.

C. Animals

Osborne-Mendel rats, procured from Battelle Memorial Institute, Columbus, Ohio, and B6C3F1 hybrid mice (C57B1/6 female x C3H/He male), procured from Charles River Breeding Laboratories, Inc., Wilmington, Massachusetts, were used in this study. Upon receipt both species were quarantined for 7-10 days, determined to be free from observable disease or parasites, and then assigned to test and control groups.

D. Animal Maintenance

All animals were housed in temperature- and humidity-controlled rooms. No other chemicals were tested, and no other rats were housed in the room in which dimethoate-treated rats and their matched controls were housed. The mice were housed in a room where dimethoate, parathion, and phosphamidon were concurrently under test. The rats were maintained individually in suspended wire cages, and the mice were housed in plastic cages with filter

caps, five per cage for females, and two to three per cage for males. Initially, rats were transferred to clean cages once per week; later in the study, cages were changed every 2 weeks. Cages for mice were changed weekly. Absorbent sheets under the rat racks were changed three times per week. Animal racks were rotated laterally for both species at weekly intervals; at the same time, each cage was changed to a different position in the row within the same column.

E. Subchronic Toxicity Test

Feeding studies were conducted to evaluate subchronically the toxicity of dimethoate in order to establish the maximum tolerated doses (MTD) for administration in the chronic study. The low dose was one-half of the MTD. Dimethoate was added to the animal feed at twofold increasing concentrations, starting with 62.5 ppm and ending with 4,000 ppm. The compound was provided in feed to experimental groups of five male and five female rats and mice for 6 weeks followed by a 2-week observation period.

In both male and female rats, at 250 and 500 ppm, weight depression was apparent during the first weeks. Later these animals apparently adapted, and weight gains approached those of the controls. There was no mortality at these dosages; however,

all rats receiving 1,000 ppm died. The high and low doses for rats were therefore set at 500 and 250 ppm.

In mice, the males initially lost weight at 500 ppm; however, male mice at 250 ppm and female mice at both 250 and 500 ppm gained weight normally. No deaths occurred in either sex at doses of 250 or 500 ppm. There were also no deaths at 1,000 ppm. The high and low doses were set at 1,000 and 500 ppm for mice.

F. Design of Chronic Studies

The design of the chronic study, including both test and matched-control groups, is illustrated in table 1.

The pooled-control group, not shown in table 1, initially consisted of the matched controls for dimethoate plus the matched controls for the studies of aldrin, chlordane, dichlorvos, dieldrin, and heptachlor; these studies overlapped the dimethoate feeding study for at least a year. Because additional matched controls were started simultaneously with restarted treatment groups for some of these compounds, the total number of pooled-control animals varied. All treated and pooled-control animals were placed on study as weanlings at 35 days of age except for the matched-control rats for dichlorvos. Because dichlorvos was the last bioassay of this series to be started, there were slight differences in the dichlorvos matched-control rats pooled

Table 1. Design of Dimethoate Chronic Feeding Study in Rats and Mice

Experimental Design	Initial No. of Animals[a]	Dimethoate in Diet[b] (ppm)	Time on Study Treated (weeks)	Time on Study Untreated (weeks)	Time-Weighted Average Dose[e] (ppm)
RATS					
Male					
Matched Control	10	0	0	114	
Low	50	250	19		155
		125	61		
		0		34-35	
High	50	500	19		
		250	61		310
		0		33-34	
Female					
Matched Control	10	0	0	114	
Low	50	250	43		
		125	37		192
		0		34-35	
High	50	500	43		
		250	37		384
		0		33-34	
MICE					
Male					
Matched Control	10[f]	0	0	94	
Low	50	250	69		250
		0		24	
High	50	500	60		500
		0		34	
Female					
Matched Control	10	0	0	94	
Low	50	250	80		250
		0		13	
High	50	500	80		500
		0		14	

[a] All animals were 35 days of age when placed on test.

[b] Initially 1,000 and 500 ppm of dimethoate were fed to mice of each sex; these doses were too toxic, however, and the mouse study was terminated and restarted as shown in the table.

[c] Doses shown were toxic; therefore, doses for treated rats were lowered and fed at concentrations shown for the varying treatment periods indicated.

[d] When diets containing dimethoate were discontinued, treated rats and their matched controls were fed plain feed diets (without corn oil) for 8 weeks, then control diets (2% corn oil added) for an additional 25 to 27 weeks. Mice received the control diet until termination.

[e] Time-weighted average dose = $\frac{\Sigma(\text{dose in ppm} \times \text{no. of days at that dose})}{\Sigma(\text{no. of days receiving each dose})}$.

[f] Examination at necropsy subsequently revealed that 3 of 10 mice designated as male matched controls were females.

for use as controls in the dimethoate study: (1) half of the animals of each sex were started on test at 43 days of age and half at 36 days of age; (2) they were obtained from the Charles River Breeding Laboratories, Inc. and were the progeny (third generation) of a group of Osborne-Mendel rats which were purchased from the Battelle Memorial Institute, Columbus, Ohio. Thus there was no significant genetic drift influencing the incidence of tumors.

G. Clinical and Pathologic Examinations

All animals were observed for signs of toxicity twice daily, and body weights were recorded at regular intervals until 110 weeks for rats and 90 weeks for mice. All animals were palpated for masses at each weighing. Those animals appearing moribund at the time of clinical examination were killed and necropsied. In the chronic study, the following 23 tissues and organs were taken from killed animals and, where feasible, from animals found dead: brain, pituitary, lymph nodes (cervical and mesenteric), thyroid, parathyroid, salivary glands, lung, heart, diaphragm, stomach (pylorus and fundus), duodenum, jejunum or ileum, large intestine, pancreas, adrenal, kidney (longitudinal and transverse), liver, skin, entire gonads, urinary bladder, prostate or uterus, and femur with marrow. Tissues were preserved in 10% buffered formalin, embedded in paraffin, sectioned, routinely stained with

hematoxylin and eosin, and histologically examined. Selected tissues were subjected to special staining techniques for more definitive diagnosis.

The intent of the histologic examination was to evaluate all organs, tissues, and gross lesions for every animal as specified in the pathology protocol for the Bioassay Program. However, occasional tissues were missing from some animals, and an occasional animal was missing or judged to be in such an advanced state of autolysis as to preclude histopathologic interpretation and was not preserved for such purposes.

H. Data Recording and Statistical Analyses

Pertinent data for this experiment have been recorded in an automatic data processing system, the Carcinogenesis Bioassay Data System (Linhart et al., 1974). The data elements include descriptive information on the chemicals, animals, experimental design, clinical observations, survival, animal weight, and individual pathologic results as recommended by the International Union Against Cancer (UICC) (Berenblum, 1969). Data tables were generated for statistical review and verification of data transcription.

Statistical analysis of the incidence of tumors was made using the Fisher exact test (Cox, 1970) to compare both the pooled

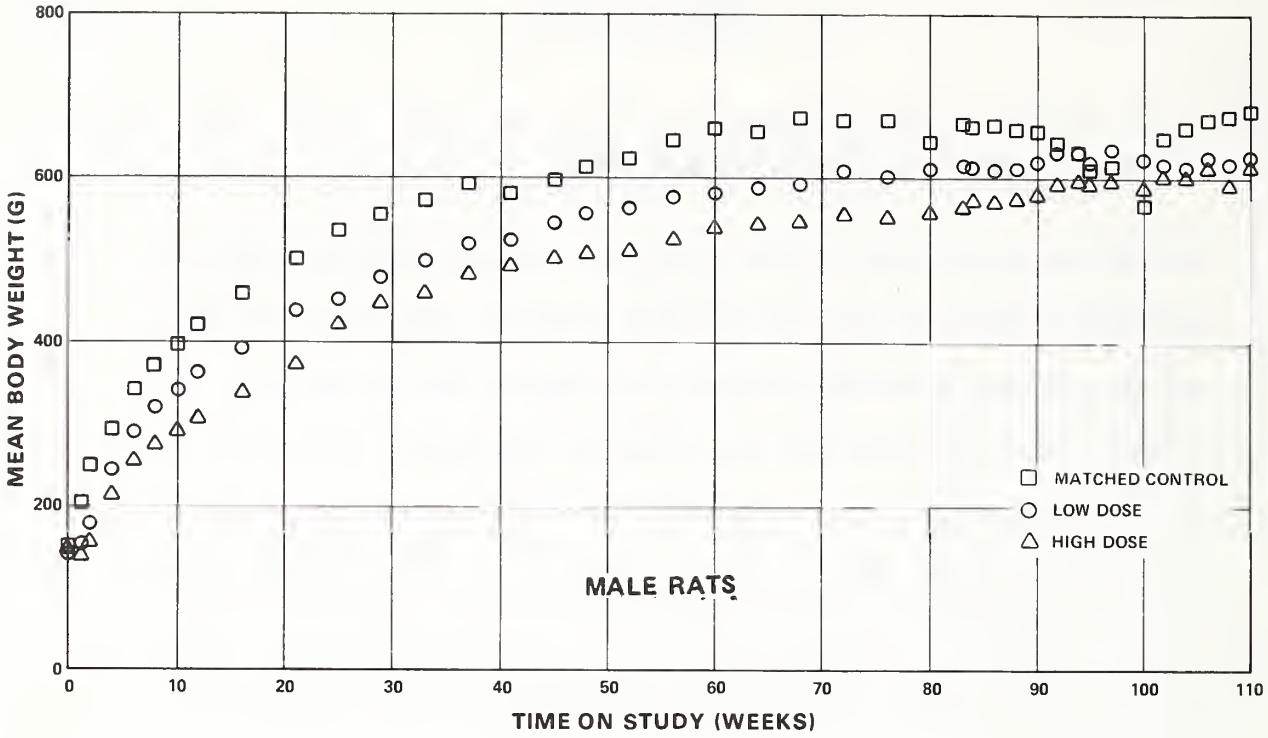
controls and the matched controls to treated animals at each dose level. In addition, the Armitage and Cochran test for linear trend in proportions with continuity correction (Armitage, 1971) was used. This test, assuming a linear trend, determines if the slope of the dose-response curve is different from zero ($P < 0.05$). The method also calculates the probability level of a departure from linear trend.

A conservative adjustment, the Bonferroni inequality (Miller, 1966), was used for simultaneous comparisons of several treatments with a control. For the comparison of k doses with a control, this correction requires a significance level less than or equal to $0.05/k$ for the overall comparison to be significant at the 0.05 level. This adjustment was made in the tables where the Fisher exact test results are shown and is discussed in the analysis when appropriate. Thus, a corrected P value < 0.05 would be deemed significant.

A. Body Weights and Clinical Signs (Rats)

During the first year of the study the average gain in weight of all treated rats, except the low-dose females, was less than that of the matched controls (figure 1). During the second year the average weight of the low-dose females was higher than that of the matched controls. Throughout the study the average weight of the high-dose females was less than that of the low-dose and control females. There appeared to be a dose-related weight depression in both low-dose and high-dose male rats throughout the study.

During the first 4 months of the study the appearance and behavior of the low-dose male and female rats generally were comparable to those of the matched controls. During the first week of the study the majority of the high-dose males and females evidenced signs considered typical of organophosphate intoxication. The animals were generally hyperexcitable, and displayed tremors and, occasionally, convulsions particularly in response to acoustic stimuli. These tremors were accompained by depression of body weight and low consumption of food. Among the high-dose male group the tremors increased during the second week, although food consumption and body weights increased.



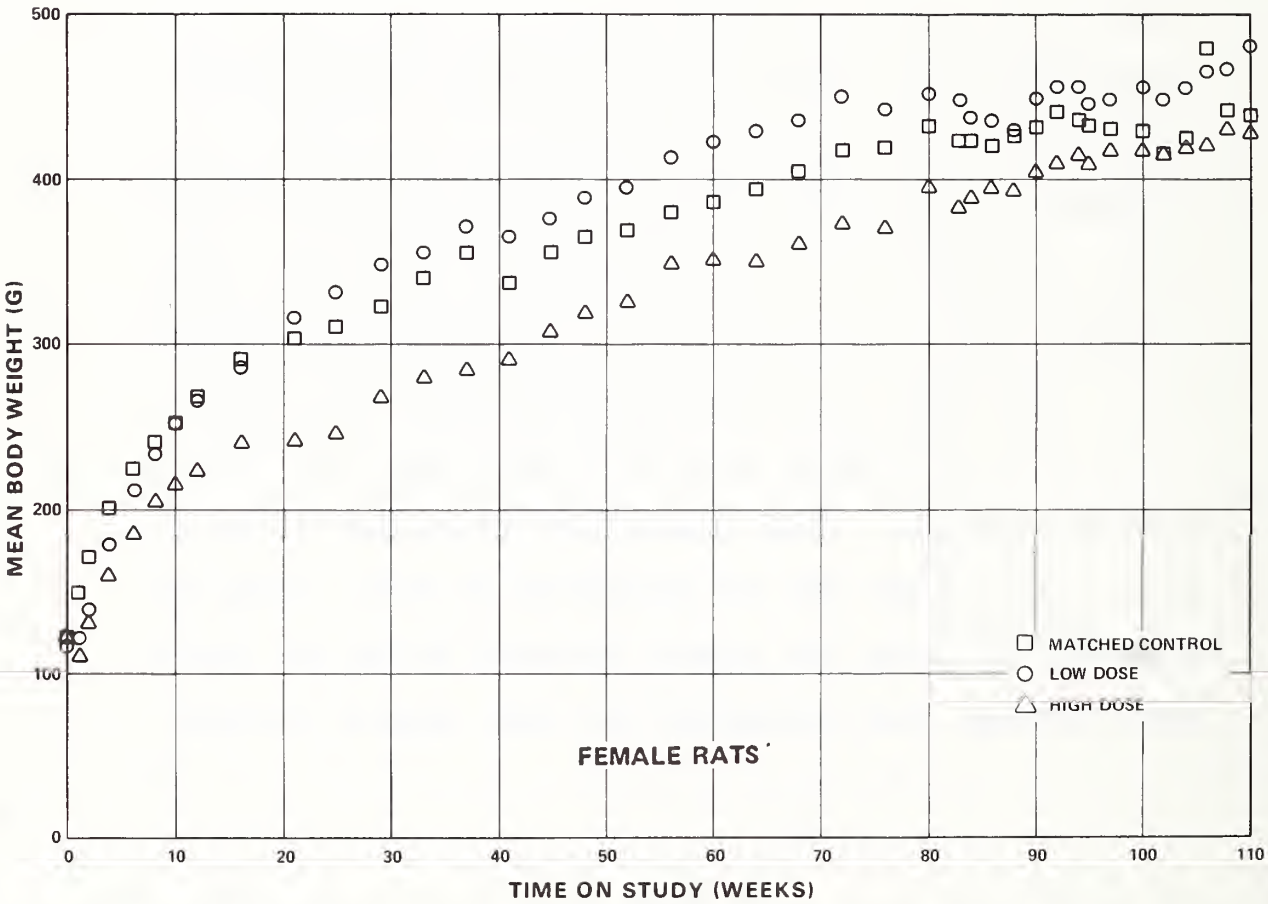


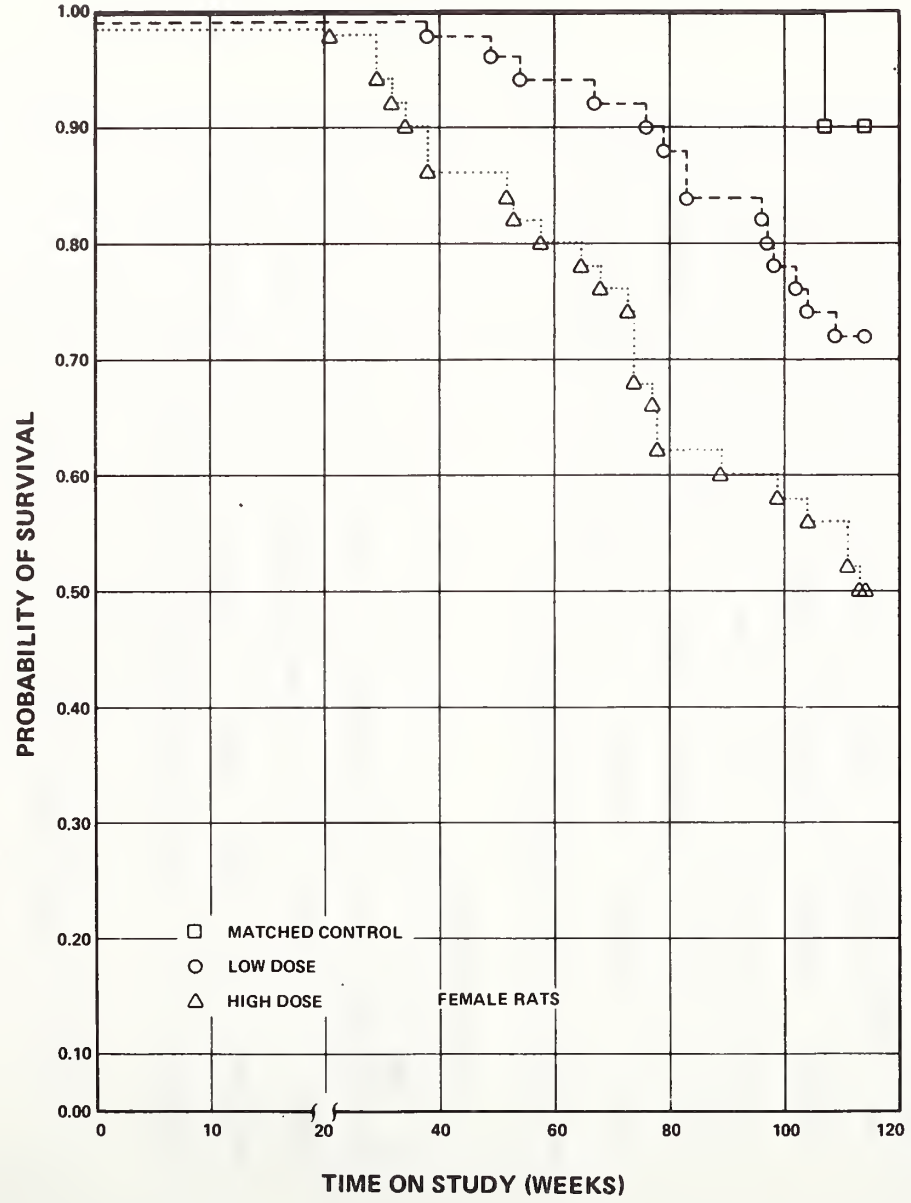
Figure 1. Growth Curves of Rats Fed Dimethoate in Diet

After the second week the tremors were no longer observed. At week 35, 80 to 90% of the treated rats, 60% of the male matched controls, and 40% of the female matched controls evidenced enlarging and protruding eyeballs with a developing opacity of the corneal surface. In some cases there was a definite thickening of the palpebral conjunctival membranes. Two rats, one high-dose female and one low-dose female, were killed for diagnostic purposes at week 38 and found to have conjunctivitis thought to be of viral origin. No deaths were attributed to this condition; however, some rats became blind in one or both eyes.

Adverse clinical signs in all treatment groups were noted at a low or moderate incidence during the second year of the study. These signs included rough and discolored (yellow) hair coats, alopecia, diarrhea, epistaxis, anemia, and tumors, as described in the pathology narrative, below. A few of the high-dose rats (male and female) evidenced dyspnea. Some treated females had vaginal bleeding. Animals that survived to termination were generally in poor physical condition.

B. Survival (Rats)

The survival data are presented in table 2 and figure 2. The two female rats killed for diagnostic purposes during week 38 are included in the data shown in figure 2. At termination there appeared to be a dose-related effect with dimethoate, but this



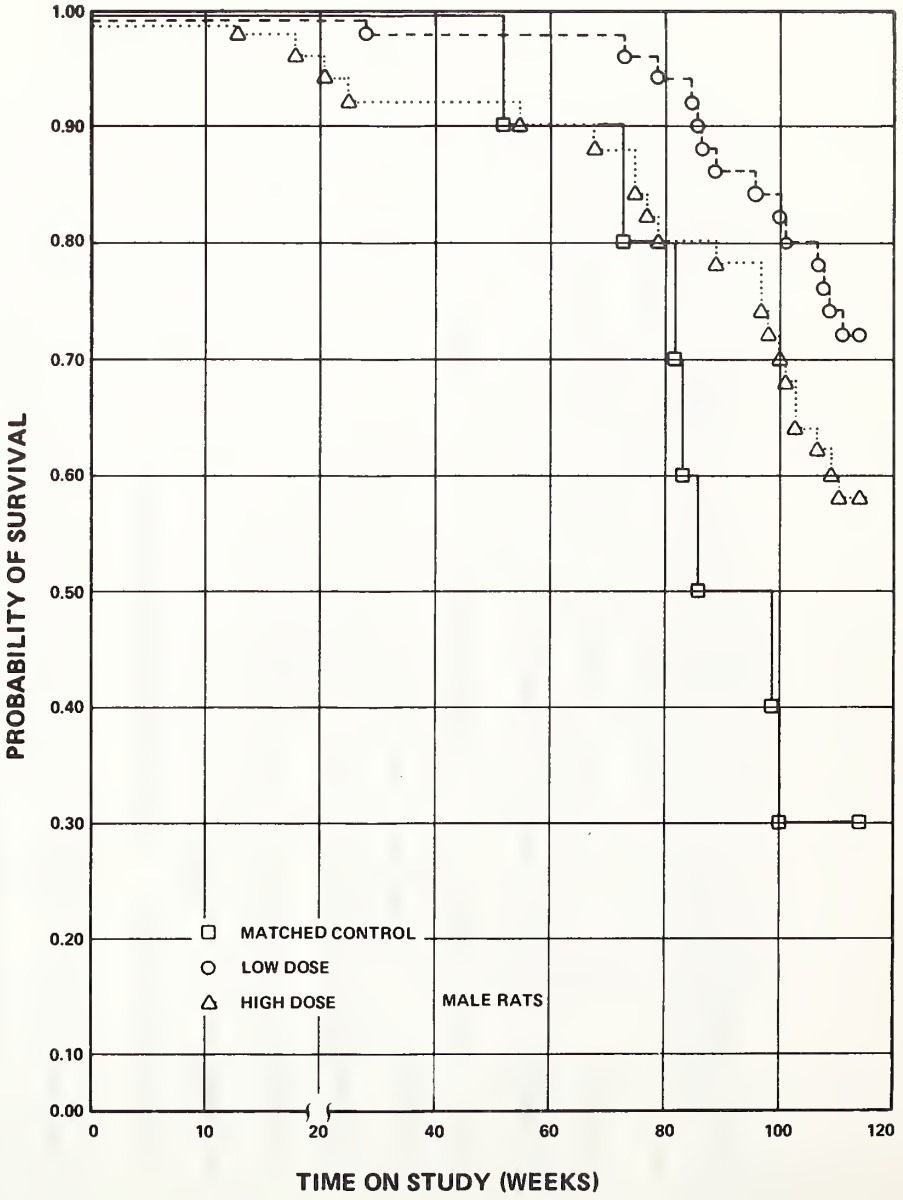


Figure 2. Survival Curves of Rats Fed Dimethoate in Diet

was obscured by the unusually large number of deaths in the male control group.

Table 2. Dimethoate Chronic Feeding Study: Number and Survival of Tumor-Bearing Rats

Sex	Dosage Group[a]	Effective Number[b]	Number TBA[c]	Percent Surviving[d] (weeks) 52	78	115[e]
M	Pooled Control	58	36	92	87	47
M	Matched Control	10	7	100	80	30
M	Low	50	23	98	96	72
M	High	49	24	92	82	58
F	Pooled Control	60	43	97	95	73
F	Matched Control	10	7	100	100	90
F	Low	47	30	98	92	74
F	High	45	21	88	67	51

[a]See table 1 for actual dosage and for schedule of dosage changes.
[b]Total number of rats initially placed on test minus the number missing or autolyzed.
[c]Number of tumor-bearing rats.
[d]Denominator for survival percentages was the original number of animals minus those killed for diagnostic purposes. No animals were accidentally killed and none were missing.
[e]Study terminated at 115 weeks.

C. Pathology (Rats)

Histopathologic findings are tabulated in Appendix A. The denominator for any particular tissue represents the number examined, and does not necessarily represent the number of animals that were placed on experiment in each group. The

numerator represents the number of animals bearing a given tumor; percentages and P values are also provided.

Numerous inflammatory, degenerative, and proliferative lesions, commonly seen in aged rats, occurred with approximately equal frequency in compound-treated and control animals. These included hepatocytomegaly, biliary hyperplasia, chronic nephritis with scarring, tubular dilatation and regeneration, C-cell hyperplasia of thyroid, and testicular atrophy.

Several nonneoplastic lesions occurred more frequently in test rats than in controls and may have been related to exposure to the test compound. These included aggregates of alveolar macrophages in lung sections, interstitial fibrosis of myocardium, focal cytomegaly of adrenal cortex, fatty metamorphosis of hepatocytes, focal follicular-cell hyperplasia in thyroid sections, and granulomas observed in the skin and subcutis of the feet.

The pituitary and thyroid were the most common primary sites of neoplasia in both test and control rats. Primary tumors occurred in the pituitary of 39/100 (39.0%) rats examined microscopically from pooled-control male rats, 7/18 (38.8%) of matched-control rats, and 47/171 (27.5%) of dimethoate-treated rats. While no follicular-cell tumors occurred in the thyroid glands examined microscopically from seven matched-control male rats, follicular-

cell tumors were observed in 4/51 (7.8%) pooled-control males and in 9/92 male test rats, an incidence of 9.8%. In female rats, the incidence of follicular-cell tumors was 3/59 (5.2%) in pooled controls; 1/10 (10.0%) in matched controls; and 3/86 (3.4%) in dimethoate-fed animals. The overall incidence of C-cell tumors was much higher than that of follicular-cell tumors; however, no difference in incidence was evident between the control and test groups.

Microscopically, the follicular-cell adenomas appeared as well-circumscribed, usually single, masses composed of enlarged follicles lined by hyperbasophilic follicular cells. Follicular cells were increased in number, either by papillary infolding of simple cuboidal or columnar epithelium into the follicular lumen, or by stratification of follicular cells surrounding the lumen. There was distinct compression of surrounding normal thyroidal parenchyma, usually with some evidence of fibrous encapsulation. Follicular-cell lesions were classified as carcinoma based upon the presence of anaplasia and histologic arrangement in disorderly nests and/or sheets. Areas with papillary patterns also occurred frequently. Fibrous stroma often intermingled with, but did not encapsulate, the tumors. C-cell lesions were classified as adenomas when the proliferating C-cells were in nodular masses that widely separated thyroidal follicles and distorted the normal follicular architecture. In the large, more

discrete nodular lesions, the proliferating C-cells were present as interlacing bundles of elongated, spindling cells, rather than exhibiting the polyhedral to spherical shape characteristic of normal C-cells. When invasion of thyroid capsule, adjacent tissues, or vessels occurred, the lesion was called C-cell carcinoma.

No mammary gland tumor was observed in 10 matched-control male rats necropsied; of 58 pooled-control males necropsied, one had a fibroma. Among 99 male dimethoate-treated rats necropsied, fibromas were observed in two animals from the low-dose group. One fibroadenoma of the mammary gland was present in 10 matched-control female rats necropsied; 8 fibroadenomas, 1 fibroma, and 2 adenocarcinomas of the mammary gland occurred in 60 pooled-control female rats necropsied: a total incidence of mammary tumors of 18.3%. Among 47 female test rats necropsied from the low-dose group, 7 had mammary tumors, an incidence of 14.8%. These included five with fibroadenomas, one with a fibroma, and one with an adenocarcinoma. In the high-dose female group, 4 mammary tumors occurred among 47 rats necropsied, an incidence of 8.5%. These included three with fibroadenomas and one with fibroma.

A summary of proliferative hepatocytic lesions observed is presented in Appendix A. These lesions appeared with approxi-

mately equal frequency in both the test and control groups. Included under the classification of focal hyperplasia were foci of hepatocytes with increased cytoplasmic basophilia and large vesicular nuclei with prominent nucleoli. These foci did not compress adjacent tissue and usually were less than 1 lobule in diameter. Lesions classified as hepatocytomegaly consisted of foci of enlarged hepatocytes, many of which contained large, vesicular nuclei and numerous fine cytoplasmic vacuoles which gave the cytoplasm a "ground glass" appearance. Distortion of lobular architecture in these foci was minimal, and trabeculae were continuous with adjacent normal hepatocytes. Lesions classified as "neoplastic nodules" had similar cytologic features, but usually were larger and contained more distinct distortion of lobular architecture; trabeculae at the periphery of these nodules were oriented perpendicular to trabeculae in adjacent normal hepatic parenchyma. Compression of adjacent parenchyma by the nodule was evident. Hepatocellular carcinoma was diagnosed when the hepatocytic lesion contained areas of complete loss of normal lobular architecture. The most frequent abnormality in this type of lesion was the presence of widely dilated sinusoidal spaces lined by rows or nests of hepatocytes several cells thick, sometimes with papillary projections of hepatocytes into the space. Pseudo-acinar formation and solid sheets of hepatocytes were less frequently observed.

A low incidence of various other types of neoplasms which occur in aged laboratory rats was observed in test and control groups with approximately equal frequency. These included islet-cell adenomas of the pancreas; hemangiomas and hemangiosarcomas of the spleen and other organs; benign and malignant primary tumors of kidney, the adrenal cortex, and male and female genitalia; malignant fibrous histiocytomas of peritoneal surfaces and subcutis; and gliomas of the brain. Bone marrow was examined, and no differences were found between the test and matched-control rats of either sex.

There were instances in this study where neoplastic or hyperplastic changes occurred only in test animals, or with increased frequency when compared to control groups. In the experience of the pathologist, however, the nature, incidence, and severity of the lesions observed provided no evidence of a carcinogenic effect.

For a summary of the incidence of nontumor pathology in rats treated with dimethoate, see Appendix C.

D. Statistical Analyses of Results (Rats)

Data from various tissues were analyzed statistically and are shown in Appendix A. Several statistics should be noted. The incidence of thyroidal follicular-cell hyperplasia of the male

dimethoate-treated rats had a dose-related increase when compared to the pooled controls, while pituitary adenomas had a dose-related decrease in the female treated animal groups when compared to the pooled-control group. None of these findings is considered to have biological significance. Given the variability of observed spontaneous incidence of these lesions in this strain of rats among laboratories and the opposite and inconsistent effects between female and male rats in this study, these findings probably are not treatment related. The dimethoate-treated animals have a significantly lower incidence of hepatocytomegaly than the pooled-control groups. The importance of this observation is difficult to evaluate. There was no statistically significant increase in the incidence of tumors in the treated group versus the control group based on data from the histopathologic examination of the tissues.

IV. RESULTS - MICE

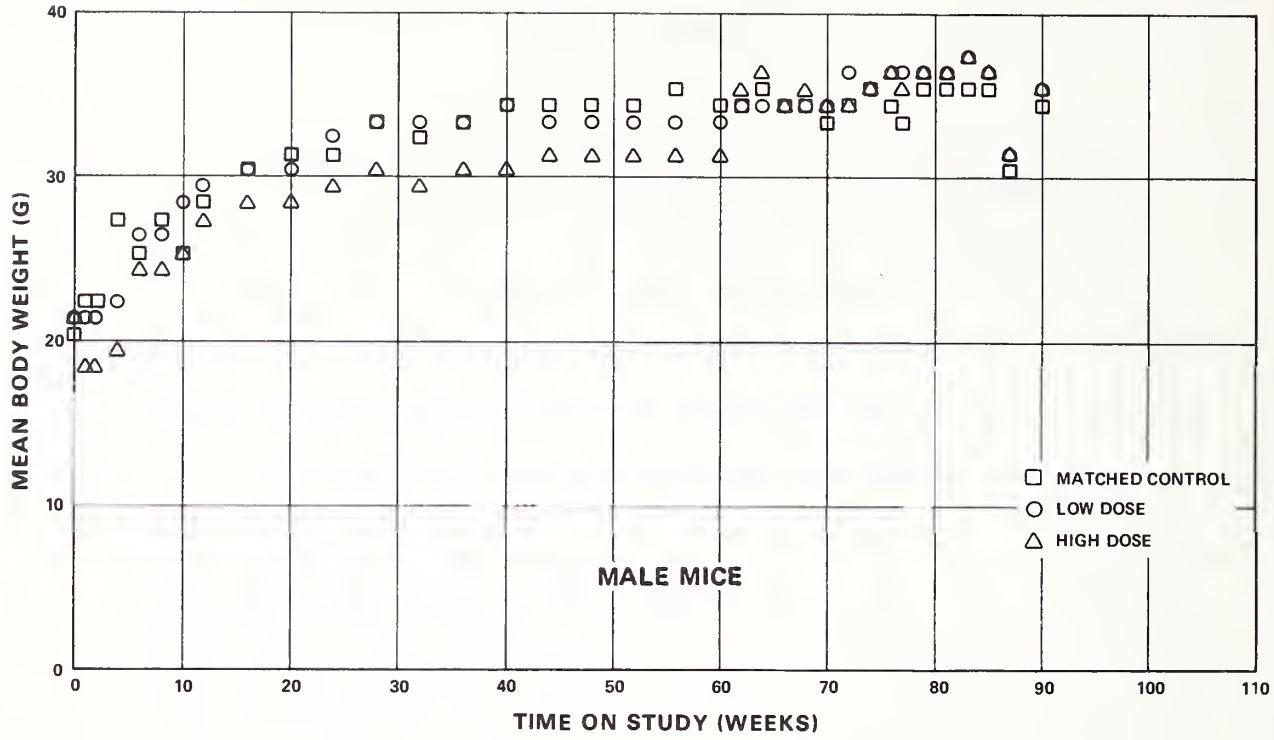
A. Body Weights and Clinical Signs (Mice)

In the first year of the study the average gain in weight of all groups except the low-dose female mice was less than that of the matched controls. In the second year the average gains in weight in the treated groups were generally similar (see figure 3).

During the first 4 months of the study the appearance and behavior of the treated mice (males and females) were generally comparable to those of the matched controls with the exception of the high-dose female group. Generalized tremors which appeared to be accompanied by rapid heartbeats were observed in this group at week 16. There was no weight depression for the female high-dose group at this time, although food consumption declined slightly.

From week 48 to week 53 some of the low-dose males were noted to have slight generalized tremors. During this period a weight depression occurred, but the food consumption remained similar to that of the control group.

At week 48 a majority of the high-dose males were observed to have generalized tremors which appeared to be accompanied by rapid heartbeats. These tremors persisted in some individual



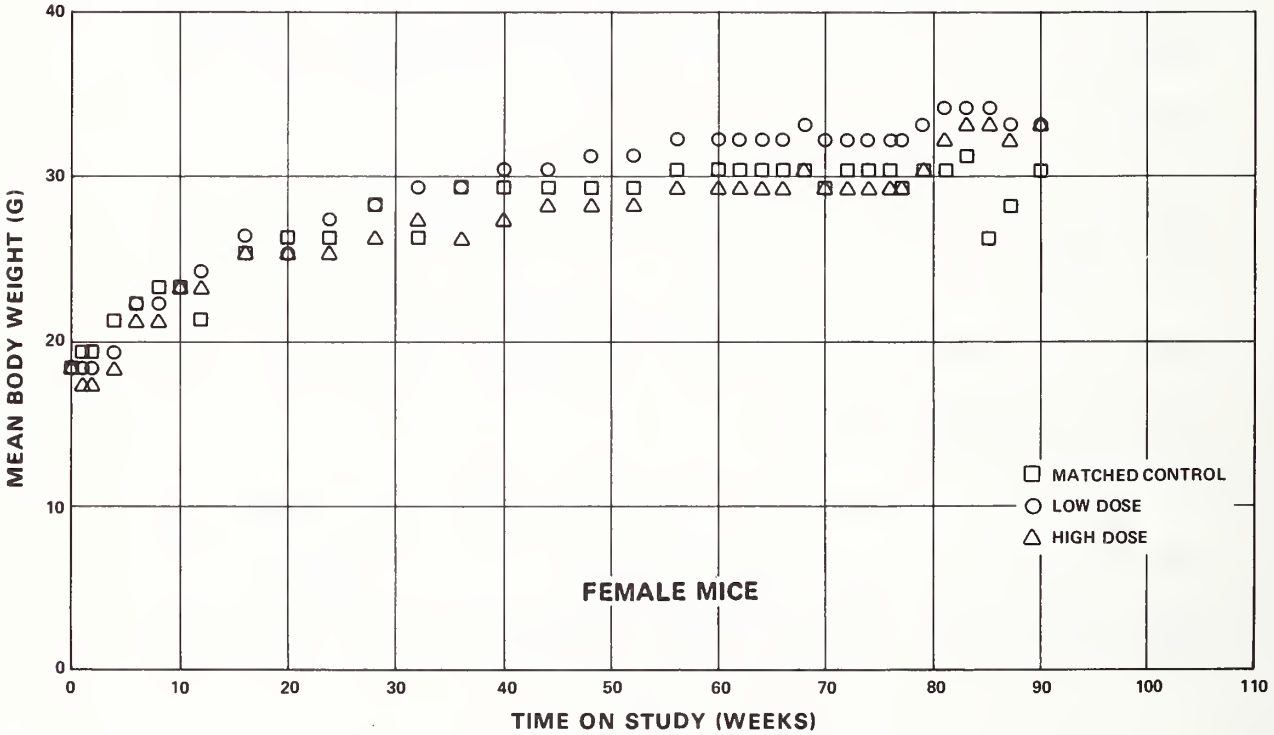


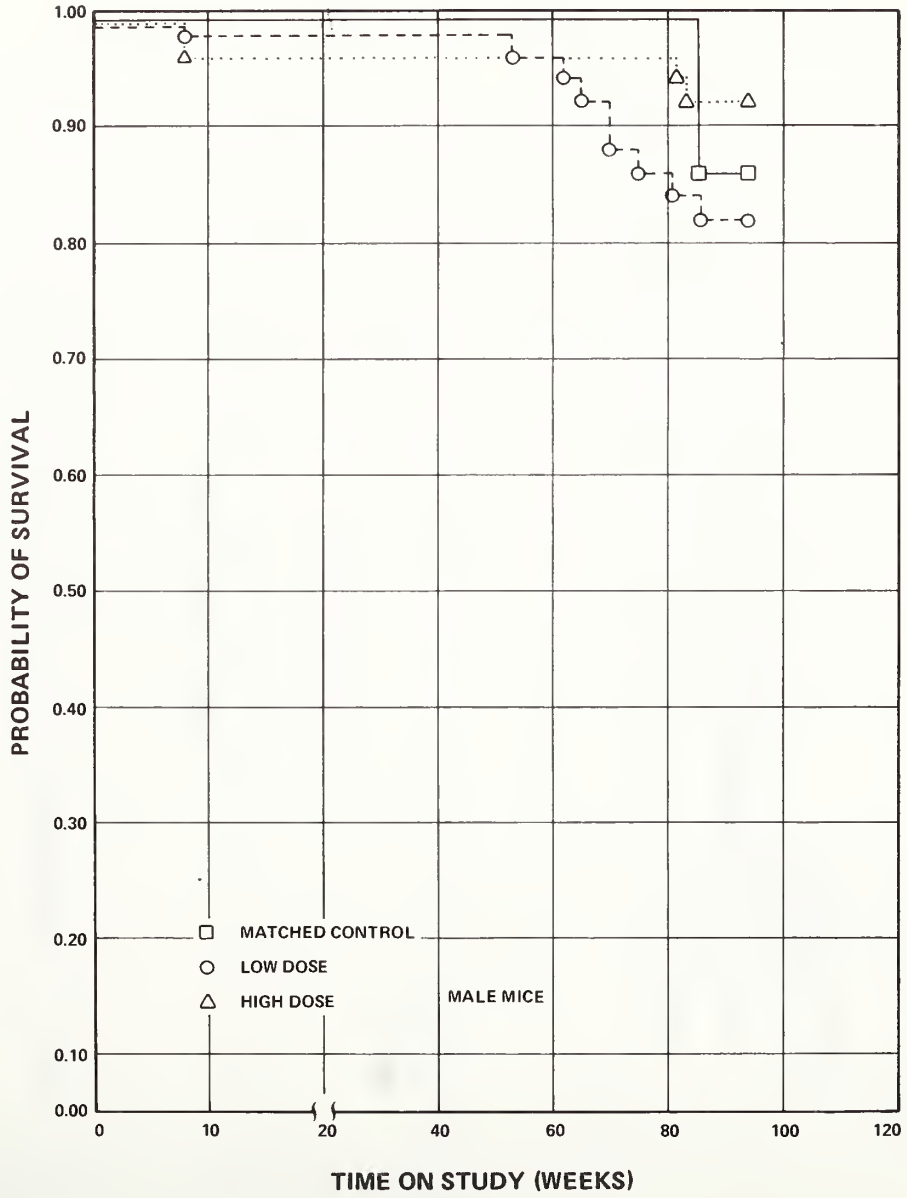
Figure 3. Growth Curves of Mice Fed Dimethoate in Diet

mice until termination but were not noted after week 48 for the majority of the group. There was no appreciable change in weight in this group from week 40 to week 60, although the consumption of food remained within a normal range.

During the second year of the study adverse clinical signs such as alopecia (generalized and/or localized), bloating or abdominal distention, and tumors were observed in all treatment groups. However, they were predominantly visible in the low-dose males and females. The high-dose mice, especially the males, had rough hair coats and, in some cases, hunched appearances. Animals surviving at termination were generally in very poor physical condition.

B. Survival (Mice)

The survival data are presented in table 3 and figure 4. The data indicate that dimethoate had no effect on mouse survival rates.



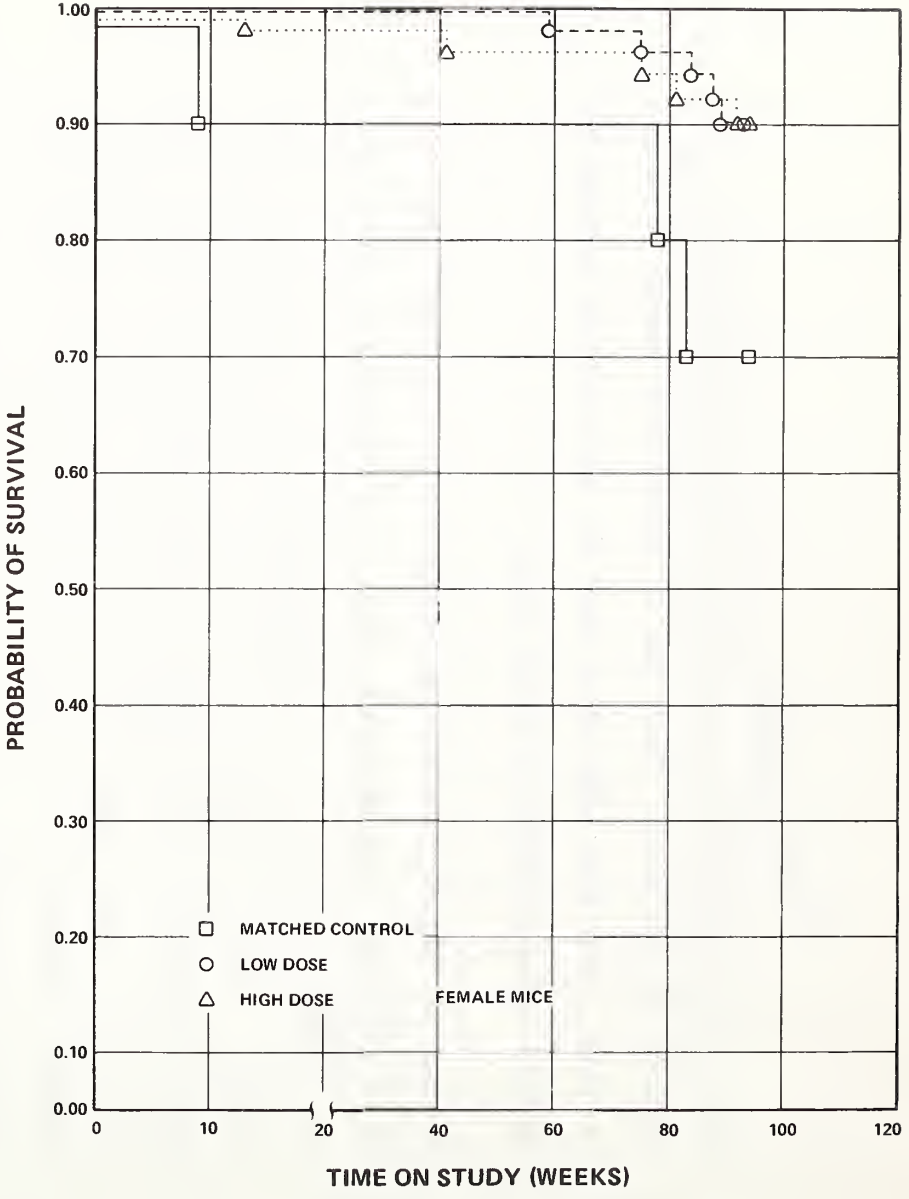


Figure 4. Survival Curves of Mice Fed Dimethoate in Diet

Table 3. Dimethoate Chronic Feeding Study:
Number and Survival of Tumor-Bearing Mice

Sex	Dosage Group[a]	Effective Number[b]	Number TBA[c]	Percent Surviving[d] (weeks) 52	78	90[e]
M	Pooled Control	96	31	94	92	85
M	Matched Control	7	6	100	100	86
M	Low	50	11	98	84	82
M	High	50	11	96	96	92
F	Pooled Control	80	14	96	90	83
F	Matched Control	10	3	90	90	70
F	Low	50	15	100	96	90
F	High	49	12	96	94	90

[a]See table 1 for actual dosage and for schedule of dosage changes.
[b]Total number of mice initially placed on test minus number missing or autolyzed.
[c]Number of tumor-bearing mice.
[d]Denominator for survival percentages was the original number of animals placed on test. No animals were accidentally killed and none were missing.
[e]Study terminated at 90 weeks.

C. Pathology (Mice)

At the beginning of the study there were 50 mice of each sex at each dosage level and 10 female and presumably 10 male matched-control mice. At necropsy, however, 3 of the 10 mice designated as "male" matched controls were found to be females. Tissues from these three mice were not included in the summary of the histopathology data; there were, therefore, only seven matched-control male mice in this study.

Histopathologic findings are tabulated in Appendix B. The denominator for any particular tissue represents the number examined and does not necessarily represent the number of animals that were placed on experiment in each group. The numerator represents the number of animals bearing a given tumor; percentages and P values are also provided.

Several nonneoplastic proliferative or inflammatory conditions occurred with approximately equal frequency in control and dimethoate-treated mice. These included lymphoid hyperplasia of the spleen, purulent inflammation of the ovary and endometrium, endometrial hyperplasia, and nodular hyperplasia of the liver. Adrenocortical hyperplasia occurred frequently in all male mice, but at a higher incidence in treated animals.

The most commonly occurring neoplasm in male mice was hepatocellular carcinoma. There were 8/50 (16%) among low-dose males and 6/50 (12%) among high-dose males, compared with 4/7 (57%) in matched controls and 17/92 (18%) in pooled controls. Female mice had a much lower incidence of this neoplasm; no primary hepatic tumor was observed in livers examined histologically from 99 female dimethoate-treated mice. Among matched controls the incidence was 1/10 (10%) and among pooled controls 3/78 (4%). The term "hepatocellular carcinoma" was used for proliferative lesions of the livers in mice which, in the judgment of the

pathologist, had the potential for progressive growth, invasion, and metastasis, and for causing death of the host. This judgment was based upon the cytologic and histologic features of the neoplasms and the knowledge that lesions with the same morphologic characteristics have exhibited malignant biologic behavior. The hepatocellular carcinomas observed in the various test and control groups comprised the full spectrum of morphology of this entity. The tumors varied from those composed of well-differentiated hepatocytes with a relatively uniform arrangement to those which were very anaplastic and poorly differentiated with numerous mitotic figures. Various types of hepatocellular carcinomas described in the literature were seen, including those with an orderly cord-like arrangement of neoplastic cells, those with a glandular pattern resembling adenocarcinoma, and those composed of sheets and nests of highly anaplastic cells intermingled with widely dilated sinusoids.

Malignant lymphoreticular tumors were the most common tumors in female mice. The majority of lymphoreticular neoplasms observed were classified as malignant lymphomas. There were 7/50 (14%) among low-dose females and 4/49 (8%) among high-dose females, compared with 2/10 (20%) in matched controls and 8/79 (10%) in pooled controls. One mast-cell sarcoma was observed in a low-dose female mouse; this neoplasm was in the liver, spleen, and bone marrow and was composed of ovoid cells with central

nuclei and numerous small cytoplasmic granules which stained metachromatically with toluidine blue and Giemsa stains. One hemangiosarcoma of the spleen occurred in a high-dose female mouse.

Several benign pulmonary epithelial tumors, classified as alveolar/bronchiolar adenomas to indicate possible sites of origin, occurred in both test and control groups. One alveolar/bronchiolar carcinoma occurred in a low-dose male mouse. This tumor metastasized to the bronchial lymph node and heart.

Of the primary endocrine tumors, follicular-cell adenomas of the thyroid were the most frequent, occurring with approximately equal frequency in test and control groups. One cortical carcinoma and one pheochromocytoma occurred in adrenals examined from 45 high-dose female mice; no adrenal tumor was observed in any other group.

Other tumors observed in tissues examined from mice in this study included fibrosarcomas of the skin in the male mice only (1/92 pooled controls, 1/7 matched controls, 1/50 low-dose, and 1/50 high-dose males); one carcinoma of the rete testis in a high-dose male mouse; one leiomyosarcoma of the vagina in a low-dose female mouse; two endometrial stromal polyps of the uterus; one papillary adenoma; and one thecoma of the ovary.

There were instances in this study where neoplastic or hyperplastic lesions occurred only or with increased frequency in test animals when compared to control groups. In the experience of the pathologist, however, the nature, incidence, and severity of the lesions observed provide no clear evidence of a carcinogenic effect.

For a summary of the incidences of nontumor pathology inmice treated with dimethoate, see Appendix D.

D. Statistical Analyses of Results (Mice)

Selected tissue data were analyzed statistically, and the results are shown in Appendix B. Several statistics are of interest, including pulmonary neoplasms and adrenocortical hyperplasia where one sex of the mouse had a higher incidence of lesions than the pooled controls. Neither of these findings is considered to have biological significance on the basis of the variability of observed spontaneous incidences in this strain and the opposite and inconsistent effects between male and female animals. Data from the histopathologic examination of tissues revealed no significant difference in the incidence of tumors among the dimethoate-treated mice and their controls.

V. DISCUSSION

Dimethoate is a member of the organophosphorus class of pesticides whose predominant mode of toxicity is inhibition of cholinesterase. Toxicity characteristic of these compounds was evident in the animals in this bioassay. Early in the study tremors and hyperexcitability were observed in both male and female rats. In mice, tremors also were noted in both sexes, but at a later point in the study. Other clinical signs could not definitely be related to treatment. The toxicity of dimethoate may have affected the survival of test animals, since among rats fewer of the high-dose than low-dose animals survived to termination. However, the significance of this observation is not clear, since survival was lowest in the 10 male matched-control rats.

There were instances in this study where neoplastic or hyperplastic lesions occurred only in test animals, or with increased frequency as compared to controls. However, these instances are not statistically significant, and they are not considered to be biologically significant. Thus, under the conditions of this study, dimethoate was not carcinogenic. This bioassay did provide an acceptable test for carcinogenicity under the general guidelines of the Bioassay Program since maximum doses were used

and these animals survived to an age at which tumors could have developed.

These conclusions differ from those of Gibel et al. (1973), who suggested that dimethoate may have carcinogenic properties. Because these investigators did not report in detail either their methods or their results, it is not possible to compare their data with the present study. In addition, their use of different strains of test animals, namely the Wistar rats and the AB mouse, may be significant.

VI. BIBLIOGRAPHY

Armitage, P. 1971. Statistical Methods in Medical Research, p. 135. J. Wiley & Sons, New York.

Berenblum, I., ed. 1969. Carcinogenicity Testing. UICC Technical Report Series, Vol. 2. International Union Against Cancer, Geneva.

Chemical Economics Handbook. 1969. Chemical Information Services, Stanford Research Institute, Menlo Park, California.

Cox, D.R. 1970. Analysis of Binary Data, p. 62. Methuen and Co., Ltd., London.

Gibel, W., Lohs, Kh., Wildner, G.P., Ziebarth, D., and Stieglitz, R. 1973. Experimental study on carcinogenic, hematotoxic, and hepatotoxic activity of organic phosphorus pesticides. Arch. Geschwulstforsch. 41:311-328 (translated from German).

Linhart, M.S., Cooper, J.A., Martin, R.L., Page, N.P., and Peters, J.A. 1974. Carcinogenesis bioassay data system. J. Comp. Biomed. Res. 7:230-248.

Martin, H., ed. 1971. Pesticide Manual, 2nd edition, p. 90. British Crop Protection Council.

Miller, R.G., Jr. 1966. Simultaneous Statistical Inference, p. 8. McGraw-Hill, New York.

Sontag, J., Page, N., and Saffiotti, U. 1976. Guidelines for Carcinogen Bioassay in Small Rodents. NCI Carcinogenesis Technical Report Series No. 1. National Cancer Institute, NIH, PHS, U.S. DHEW Publication No. (NIH) 76-801. U.S. Government Printing Office, Washington, D.C.

U.S. Environmental Protection Agency. 1975. Tolerances and exemptions from tolerances for pesticide chemicals in or on raw agricultural commodities - dimethoate. Federal Register 40 (206):49575.

APPENDIX A

SUMMARY OF THE INCIDENCE OF TUMORS AND PROLIFERATIVE LESIONS IN RATS FED DIMETHOATE IN THE DIET

Appendix A. Summary of the Incidence of Tumors and Proliferative Lesions in Rats Fed Dimethoate in the Diet

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Digestive System[b]								
Neoplastic Nodule	2/58 (3%)	0/10	1/49 (2%)	0/48	5/60 (8%)	1/10 (10%)	1/47 (2%)	4/44 (9%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hepatocellular Carcinoma	1/58 (2%)	0/10	0/49	1/48 (2%)	0/60	0/10	0/47	1/44 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Total Liver Neoplasms	3/58 (5%)	0/10	1/49 (2%)	1/48 (2%)	5/60 (8%)	1/10 (10%)	1/47 (2%)	5/44 (11%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Other Lesions of Liver								
Focal Hyperplasia	4/58 (7%)	0/10	1/49 (2%)	2/48 (4%)	1/60 (2%)	0/10	0/47	0/44
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hepatocytomegaly	30/58 (52%)	5/10 (50%)	19/49 (39%)	12/48 (25%)	26/60 (43%)	5/10 (50%)	4/47 (8.5%)	12/44 (27%)
P Values[c]	.003N/.818	.096N/.830	.252N/.752N	.008N/.234N	.020N/.001	.560/.001	.000N/.010N	.122N/.306N
Small Intestine								
Adenocarcinoma	0/52	0/8	0/48	1/45 (2%)	0/56	0/10	0/46	0/37
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

[a] Low- and high-dose male and female rats received "time-weighted average doses" of 155, 310, 192, and 384 ppm, respectively.
[b] Number of tumor-bearing animals/number of animals examined at site, and (%).
[c] Beneath the untreated controls incidence is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10 (otherwise N.S. - not significant) and its departure statistic (P value/departure value).
Beneath the dosed group incidence is the corrected probability level for the Fisher exact test for comparison of that dosed group with the control groups when it is below 0.10 (otherwise N.S. - not significant).(P value for pooled controls/P value for matched controls).
N = negative trend.

Appendix A. (Rats, continued)

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Urinary Tract[b]								
Kidney								
Tubular-Cell Adenoma	3/57 (5%)	1/9 (11%)	0/50	0/48	0/58	0/10	0/47	0/45
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hamartoma	0/57	0/9	0/50	1/48 (2%)	1/58 (2%)	0/10	0/47	1/45 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Malignant Mixed Tumor	0/57	0/9	1/50 (2%)	0/48 (2%)	1/58* (2%)	0/10	0/47	1/45 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Total Renal Neoplasms	3/57 (5%)	1/9 (11%)	1/50 (2%)	1/48 (2%)	2/58 (3%)	0/10	0/47	2/45 (4%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hyperplasia, Renal Pelvis	19/57 (33%)	1/9 (11%)	6/50 (12%)	11/48 (22%)	17/58 (29%)	2/10 (20%)	9/47 (19%)	8/45 (18%)
P Values[c]	.016N/.026	.114/.549	.016N/N.S.	.338N/N.S.	.095N/.544	N.S.	.332N/N.S.	.270N/N.S.
Urinary Bladder								
Epithelial Hyperplasia	12/51 (23.5%)	2/8 (25%)	4/45 (9%)	7/42 (17%)	8/53 (15%)	1/9 (11%)	2/42 (5%)	2/38 (5%)
P Values[c]	.203N/.098	.534/.154	N.S.	N.S.	.062N/.308	N.S.	N.S.	N.S.

*This neoplasm was diagnosed as a liposarcoma at microscopic examination. Several months following submission of the data from this study, a decision was made following consultation with pathologists from NCI and Tracor Jitco to classify tumors of this type as malignant mixed tumors of kidney. Therefore, this neoplasm should be included in summary of incidence of malignant mixed renal tumors.

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Endocrine System[b]								
Thyroid								
Follicular-Cell Adenoma	3/51 (6%)	0/7	4/47 (8.5%)	3/45 (7%)	2/59 (3%)	1/10 (10%)	2/46 (4%)	0/39
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Follicular-Cell Carcinoma	1/51 (2%)	0/7	0/47	2/45 (4%)	1/59 (2%)	0/10	1/46 (2%)	0/40
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Total Follicular-Cell Neoplasms	4/51 (8%)	0/7	4/47 (8.5%)	5/45 (11%)	3/59 (5%)	1/10 (10%)	3/46 (6.5%)	0/40
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	.088N/.706	N.S.	N.S.
C-cell Adenoma	3/51 (6%)	1/7 (14%)	7/47 (15%)	2/45 (4%)	7/59 (12%)	2/10 (20%)	8/46 (17%)	4/40 (10%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
C-cell Carcinoma	1/51 (2%)	0/7	1/47 (2%)	2/45 (4%)	5/59 (8%)	1/10 (10%)	3/46 (6.5%)	2/40 (5%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Total C-cell Neoplasms	4/51 (8%)	1/7 (14%)	8/47 (17%)	4/45 (9%)	12/59 (20%)	3/10 (30%)	11/46 (24%)	6/40 (15%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Total Thyroid Neoplasms	8/51 (16%)	1/7 (14%)	12/47 (26%)	9/45 (20%)	15/59 (25%)	4/10 (40%)	14/46 (30%)	6/40 (15%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	.164N/.193	.036N/.720	N.S.	N.S.

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Follicular-Cell[b] Hyperplasia	0/51	0/7	4/47 (8.5%)	7/45 (16%)	4/59 (7%)	0/10	1/46 (2%)	0/40
P Values[c]	.003/.776	.116/.863	.098/N.S.	.008/N.S.	N.S.	N.S.	N.S.	N.S.
C-cell Hyperplasia	29/51 (57%)	5/7 (71%)	21/47 (45%)	23/45 (51%)	30/59 (51%)	5/10 (50%)	22/46 (48%)	14/40 (35%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	.069N/.606	N.S.	N.S.	N.S.
Other Endocrine Tissues								
Pituitary								
Adenoma	14/49 (29%)	1/8 (12.5%)	13/46 (28%)	9/41 (22%)	23/51 (44%)	5/10 (50%)	15/45 (33%)	8/39 (20.5%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	.012N/.817	.039N/.787	.374N/.524N	.030N/.146N
Carcinoma	2/49 (4%)	1/8 (12.5%)	0/46	1/41 (2%)	0/51	0/10	1/45 (2%)	0/39
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Adrenal								
Cortical Adenoma	2/55 (4%)	0/9	0/49	0/44	0/56	0/8	1/46 (2%)	1/43 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Cortical Carcinoma	1/54 (2%)	0/9	1/49 (2%)	1/44 (2%)	0/56	0/8	1/46 (2%)	1/43 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Pancreas								
Islet-Cell Adenoma	1/52 (2%)	0/7	1/49 (2%)	3/44 (7%)	1/60 (2%)	1/10 (10%)	4/46 (9%)	0/42
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Appendix A. (Rats, continued)

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Reproductive System[b]								
Testis								
Interstitial-Cell Tumor	0/58	0/10	2/50 (4%)	1/49 (2%)	---	---	---	---
P Values[c]	N.S.	N.S.	N.S.	N.S.				
Uterus								
Endometrial Stromal Polyp	---	---	---	---	6/57 (11%)	1/9 (11%)	1/46 (2%)	3/44 (7%)
P Values[c]					N.S.	N.S.	N.S.	N.S.
Squamous-Cell Carcinoma	---	---	---	---	0/57	0/9	0/46	1/44 (2%)
P Values[c]					N.S.	N.S.	N.S.	N.S.
Ovary								
Granulosa-Cell Tumor	---	---	---	---	1/58 (2%)	1/10 (10%)	0/45	0/40
P Values[c]					N.S.	N.S.	N.S.	N.S.
Mammary Gland								
Adenocarcinoma	0/58	0/10	0/50	0/49	2/60 (3%)	0/10	1/47 (2%)	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Fibroma	1/58 (2%)	0/10	2/50 (4%)	0/49	1/60 (2%)	0/10	1/47 (2%)	1/47 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Fibroadenoma [b]	0/58	0/0	0/50	0/49	8/60 (13%)	1/10 (10%)	5/47 (11%)	3/45 (6%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Total Mammary Neoplasms	1/58 (2%)	0/0	2/50 (4%)	0/49	11/60 (18%)	1/10 (10%)	7/47 (15%)	4/47 (8.5%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Vascular and Hematopoietic Tissues								
Hemangioma	0/58	0/10	0/50	1/49 (2%)	0/60	0/10	0/47	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hemangiosarcoma	3/56 (5%)	3/10 (30%)	1/50 (2%)	2/49 (4%)	0/60	0/10	1/47 (2%)	0/47
P Values[c]	N.S.	.046N/.003	N.S./.026N	N.S./.060N	N.S.	N.S.	N.S.	N.S.
*Malignant Lymphoma	1/58 (2%)	0/10	0/50	1/49 (2%)	2/60 (3%)	0/10	0/47	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

*Includes all types.

Appendix A. (Rats, continued)

Anatomic Site and/or	Pooled Control Males	Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Control Females	Low-Dose Females	High-Dose Females
Miscellaneous Neoplasms[b]								
Trichoepithelioma	0/58	0/10	0/50	1/49 (2%)	0/60	0/10	0/47	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Lipoma	1/58 (2%)	1/10 (10%)	1/50 (2%)	1/49 (2%)	2/60 (4%)	0/10	0/47	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Osteosarcoma, Skull	0/58	0/10	1/50 (2%)	0/49	0/60	0/10	0/47	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Malignant Fibrous Histiocytoma	2/58 (3%)	1/10 (10%)	1/50 (2%)	2/49 (4%)	1/60 (2%)	0/10	1/47 (2%)	0/47
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Glioma	1/57 (2%)	0/9	0/49	1/48 (2%)	0/59	0/10	1/47 (2%)	0/45
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Alveolar/Bronchiolar Carcinoma	0/58	0/10	0/48	0/48	0/58	0/10	1/47 (2%)	0/45
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

APPENDIX B

SUMMARY OF THE INCIDENCE OF TUMORS AND PROLIFERATIVE LESIONS IN MICE FED DIMETHOATE IN THE DIET

Appendix B. Summary of the Incidence of Tumors and Proliferative Lesions in Mice Fed Dimethoate in the Diet

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Digestive System [b]								
Liver Neoplasms								
Hepatocellular Carcinoma	17/92 (18%)	4/7 (57%)	8/50 (16%)	6/50 (12%)	3/78 (4%)	1/10 (10%)	0/50	0/49
P Values[c]	.191N/.886	.024N/.043	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Nodular Hyperplasia	3/92 (3%)	0/7	3/50 (6%)	5/50 (10%)	1/78 (1%)	0/10	2/50 (4%)	2/49 (4%)
P Values[c]	.076/.840	.223/.852	N.S.	.204/N.S.	N.S.	N.S.	N.S.	N.S.
Hepatocytomegaly	0/92	0/7	2/50 (4%)	1/50 (2%)	1/78 (1%)	1/10 (10%)	0/50	4/49 (8%)
P Values[c]	N.S.	N.S.	N.S .	N.S.	.0376/.0889	N.S.	N.S.	.144/N.S.
Salivary Gland								
Fibrosarcoma	0/88	0/6	1/50 (2%)	0/49	0/77	0/10	0/50	0/49
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

[a] Low-dose and high-dose mice received 250 and 500 ppm of dimethoate in the diet, respectively.
[b] Number of tumor-bearing animals/number of animals examined at site, and (%).
[c] Beneath the untreated controls incidence is the probability level for the Armitage test for positive dose-related trend in proportions when it is below 0.10 (otherwise N.S. - not significant) and its departure statistic (P value/departure value).
Beneath the dosed group incidence is the corrected probability level for the Fisher exact test for comparison of the dosed group with the control groups when it is below 0.10 (otherwise N.S. - not significant). (P value for pooled controls/P value for matched controls).
N = negative trend.

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Endocrine System[b]								
Thyroid								
Follicular-Cell Adenoma	1/79 (1%)	1/6 (17%)	0/47	1/46 (2%)	1/72 (1%)	0/10	3/46 (6.5%)	1/41 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Follicular-Cell Hyperplasia	0/79	0/6	2/47 (4%)	1/46 (2%)	1/72 (1%)	0/10	0/46	1/41 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Adrenal								
Cortical Carcinoma	0/88	0/7	0/47	0/48	0/78	0/10	0/46	1/45 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Pheochromocytoma	0/88	0/7	0/47	0/48	0/78	0/10	0/46	1/45 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Adrenocortical Hyperplasia	27/88 (31%)	3/7 (43%)	35/47 (74%)	38/48 (79%)	19/78 (24%)	0/10	0/46	0/45
P Values[c]	.000/.020	.102/.212	.000/.202	.000/.122	.000N/.026	N.S.	.000N/N.S.	.000N/N.S.

Appendix B. (Mice, continued)

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Pulmonary[b]								
Lung								
Alveolar/Bronchiolar Carcinoma	0/91	0/7	1/50 (2%)	0/48	0/79	0/10	0/49	0/48
P Values[c]	N.S.	N.S.	N.S.	N.S	N.S.	N.S.	N.S.	N.S.
Alveolar/Bronchiolar Adenoma	6/91 (7%)	4/7 (57%)	1/50 (2%)	1/48 (2%)	0/79	0/10	4/49 (8%)	5/48 (10%)
P Values[c]	.121N/.483	.005N/.000	.310N/.000N	.336N/.002N	.007/.413	.246/.630	.040/N.S.	.014/N.S.
Total Primary Pulmonary Neoplasms	6/91 (8%)	4/7 (57%)	2/50 (4%)	1/48 (2%)	0/79	0/10	4/49 (8%)	5/48 (10%)
P Values[c]	.158N/.897	.001N/.000	.640N/.002N	.336N/.002N	.007/.414	.246/.630	.040/N.S.	.014/N.S.
Vascular and Hematopoietic								
Malignant Lymphoma*	5/92 (5%)	0 /7	0/50	2/50 (4%)	8/79 (10%)	2/10 (20%)	7/50 (14%)	4/49 (8%)
P Values[c]	N.S.	N.S.	.220N/N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Mast-Cell Sarcoma	0/92	0/7	0/50	0/50	0/79	0/10	1/50 (2%)	0 /49
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Hemangiosarcoma, Spleen	0/90	0/7	0/50	0/50	0/77	0/9	0/50	1/49 (2%)
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

*For purposes of this summary table, "malignant lymphoma" includes lymphosarcoma, reticulum cell sarcoma, and all "types" of malignant lymphoma.

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Reproductive System[b]								
Vagina								
Leiomyosarcoma	---	---	---	---	0/79	0/10	1/50 (2%)	0/49
P Values[c]					N.S.	N.S.	N.S.	N.S.
Uterus								
Endometrial Stromal Polyp	---	---	---	---	1/78 (1%)	1/9 (11%)	0/50	0/48
P Values[c]					N.S.	N.S.	N.S.	N.S.
Endometrial Hyperplasia	---	---	---	---	27/78 (35%)	0/9	10/50 (20%)	9/48 (19%)
P Values[c]					.006N/.434	.409/.226	.112N/.328	.084N/.372
Ovary								
Papillary Adenoma	---	---	---	---	0/73	0/10	0/46	1/45 (2%)
P Values[c]					N.S.	N.S.	N.S.	N.S.
Thecoma	---	---	---	---	0/73	0/10	0/46	1/45 (2%)
P Values[c]					N.S.	N.S.	N.S.	N.S.
Testis								
Carcinoma, Rete Testis	0/90	0/7	0/49	1/48 (2%)	---	---	---	---
P Values[c]	N.S.	N.S.	N.S.	N.S.				

Appendix B. (Mice, continued)

Anatomic Site and/or Body System	Pooled Control Males	Matched Control Males	Low-Dose Males	High-Dose Males	Pooled Control Females	Matched Control Females	Low-Dose Females	High-Dose Females
Integumentary System[b]								
Skin								
Fibrosarcoma	1/92 (1%)	1/7 (14%)	1/50 (2%)	1/50 (2%)	0/79	0/10	0/50	0/49
P Values[c]	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

APPENDIX C

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN RATS FED DIMETHOATE IN THE DIET

TABLE C1

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN MALE RATS FED DIMETHOATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10 (100%)	50 (100%)	49 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	49
ANIMALS WITH TUMORS	7 (70%)	23 (46%)	24 (49%)
INTEGUMENTARY SYSTEM *	1 (10%)	5 (10%)	5 (10%)
SKIN	1	5	5
INFLAMMATION SUPPURATIVE		1	
INFLAMMATION GRANULOMATOUS		4	3
INFLAMMATION FOCAL GRANULOMATOUS			2
INFLAM SUPPURATIVE GRANULAMATOUS	1		
GRANULATION TISSUE		1	
HYPERPLASIA EPITHELIAL		2	3
RESPIRATORY SYSTEM		17 (34%)	22 (45%)
TRACHEA			1
INFLAMMATION CHRONIC			1
LUNG		17	21
FOREIGN BODY		1	1
EMPHYSEMA			1
CONGESTION			1
EDEMA			1
HEMORRHAGE			3
FOREIGN-BODY PNEUMONIA			1
ABSCESS			1
ALVEOLAR MACROPHAGES		15	14
HYPERPLASIA ALVEOLAR-CELL		4	1
LUNG/ALVEOLI		1	2
INFLAMMATION SUPPURATIVE		1	2
CALCIFICATION			
CIRCULATORY SYSTEM		24 (48%)	20 (41%)
MYOCARDIUM		23	19
INFLAMMATION		1	1

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
MYOCARDIUM (CONT.)			
INFLAMMATION FOCAL			2
FIBROSIS		22	16
FIBROSIS FOCAL		1	2
DEGENERATION		1	
CALCIFICATION			
ENDOCARDIUM		2	6
FIBROSIS		2	6
AORTA		1	
CALCIFICATION		1	
MESENTERIC ARTERY		2	
PERIARTERITIS		2	
DIGESTIVE SYSTEM	7 (70%)	34 (68%)	25 (51%)
SALIVARY GLAND		2	1
INFLAMMATION FOCAL		1	1
INFLAMMATION FOCAL GRANULOMATOUS		1	
LIVER	6	21	18
CONGESTION			2
INFLAMMATION FOCAL		1	
METAMORPHOSIS FATTY		1	1
HEPATOCYTOMEGALY	5	19	12
ANGIECTASIS	1	1	4
HEMATOPOIESIS	1		
LIVER/HEPATOCYTES		1	2
HYPERPLASIA FOCAL		1	2
BILE DUCT	2	12	8
INFLAMMATION	1	2	3
FIBROSIS			1
HYPERPLASIA	2	11	6
PANCREAS		2	
INFLAMMATION ACUTE SUPPURATIVE		1	

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
PANCREAS (CONT.)			
FIBROSIS FOCAL		1	
PANCREATIC ACINUS		2	
ATROPHY		1	
ATROPHY FOCAL		1	
STOMACH		1	
ABSCESS		1	
GASTRIC MUCOSA		3	1
MULTIPLE CYSTS			1
CALCIFICATION		3	
SMALL INTESTINE		1	
INFLAMMATION FOCAL GRANULOMATOUS		1	
URINARY SYSTEM	9 (90%)	45 (90%)	35 (71%)
KIDNEY	6	44	30
INFLAMMATION CHRONIC	6	44	30
KIDNEY/CORTEX			2
CAST			1
CYTOPLASMIC VACUOLIZATION			1
RENAL TUBULE	2	1	
PIGMENTATION	1	1	
HYPERPLASIA DIFFUSE	1		
KIDNEY/PELVIS	2	7	11
CALCULUS	1	3	2
INFLAMMATION			1
HYPERPLASIA EPITHELIAL	1	6	11
URINARY BLADDER	3	5	12
CALCULUS	1	2	6

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY BLADDER (CONT.)			
HYPERPLASIA EPITHELIAL	2	4	7
ENDOCRINE SYSTEM	5 (50%)	33 (66%)	32 (65%)
PITUITARY		2	3
HYPERPLASIA CHROMOPHOBE-CELL		2	3
ADRENAL CORTEX		3	8
CYTOMEGALY		3	8
THYROID	5	25	27
ULTIMOBRANCHIAL CYST			3
CYSTIC FOLLICLES		1	2
HYPERPLASIA C-CELL	5	21	23
HYPERPLASIA FOLLICULAR-CELL		4	7
PARATHYROID	2	8	1
HYPERPLASIA	2	8	1
PANCREATIC ISLETS		1	1
HYPERPLASIA		1	1
HEMATOPOIETIC SYSTEM	1 (10%)	6 (12%)	9 (18%)
SPLEEN	1	6	8
HEMORRHAGE			1
FIBROSIS			1
FIBROSIS FOCAL		1	2
HEMOSIDEROSIS			1
HYPERPLASIA RETICULUM-CELL			4
HEMATOPOIESIS	1	5	3
LYMPH NODE		1	2
HYPERPLASIA RETICULUM-CELL		1	
LYMPHOID HYPERPLASIA			2

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM	9 (90%)	41 (82%)	36 (73%)
PROSTATE	1	9	10
INFLAMMATION	1	2	
INFLAMMATION SUPPURATIVE		7	8
INFLAMMATION GRANULOMATOUS			2
HYPERPLASIA EPITHELIAL		1	
TESTIS	9	41	35
PERIARTERITIS		2	1
ATROPHY	9	41	35
TUNICA VAGINALIS			2
HYPERPLASIA MESOTHELIAL			2
NERVOUS SYSTEM	2 (20%)	1 (2%)	
BRAIN/MENINGES	1		
INFLAMMATION FOCAL GRANULOMATOUS	1		
BRAIN	1	1	
CORPORA AMYLACEA	1	1	
MUSCULOSKELETAL SYSTEM		2 (4%)	1 (2%)
BONE		1	
OSTEOPOROSIS		1	
SKELETAL MUSCLE		1	1
INFLAMMATION SUPPURATIVE		1	
INFLAMMATION GRANULOMATOUS			1
SPECIAL SENSE ORGANS			1 (2%)
EYE			1
SYNECHIA ANTERIOR			1
EYE/CILIARY BODY			1
INFLAMMATION			1

TABLE C1 MALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
IRIS			1
INFLAMMATION			1
EYE/CRYSTALLINE LENS			1
DEGENERATION			1
ALL OTHER SYSTEMS	1 (10%)	8 (16%)	
MULTIPLE ORGANS	1	6	
PERIARTERITIS		6	
ARTERIOSCLEROSIS	1	2	
ARTERIAL CALCIFICATION		1	
CALCIFICATION	1	2	
PERITONEUM		1	
INFLAMMATION		1	
ADIPOSE TISSUE		1	
INFLAMMATION GRANULOMATOUS		1	
NO LESION REPORTED		1	
AUTOLYSIS/NO NECROPSY PERFORMED			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*	3	4	6
MORIBUND SACRIFICE	4	10	15
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	3	36	29
*INCLUDES AUTOLYZED ANIMALS			

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

TABLE C2

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN FEMALE RATS FED DIMETHOATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10 (100%)	47 (100%)	47 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	47	45
ANIMALS WITH TUMORS	7 (70%)	30 (64%)	21 (45%)
INTEGUMENTARY SYSTEM *		2 (4%)	3 (6%)
SKIN		2	3
INFLAMMATION SUPPURATIVE			1
INFLAMMATION GRANULOMATOUS		2	2
RESPIRATORY SYSTEM	2 (20%)	16 (34%)	21 (45%)
TRACHEA		1	1
FOREIGN BODY			1
INFLAMMATION CHRONIC		1	
LUNG/BRONCHIOLE	1		
INFLAMMATION SUPPURATIVE	1		
LUNG	2	15	21
ATELECTASIS		1	
CONGESTION			4
EDEMA			1
HEMORRHAGE			1
FOREIGN-BODY PNEUMONIA			5
ALVEOLAR MACROPHAGES	2	14	16
HYPERPLASIA ALVEOLAR-CELL		1	
LUNG/ALVEOLI		1	
INFLAMMATION SUPPURATIVE		1	
CIRCULATORY SYSTEM	2 (20%)	15 (32%)	9 (19%)
MYOCARDIUM	2	14	8
FIBROSIS	2	14	6
FIBROSIS FOCAL			2
ENDOCARDIUM	1	2	1
FIBROSIS	1	2	1

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
MESENTERIC ARTERY		1	
PERIARTERITIS		1	
DIGESTIVE SYSTEM	6 (60%)	26 (55%)	22 (47%)
SALIVARY GLAND		1	1
CALCULUS		1	
FIBROSIS FOCAL		1	1
LIVER	5	15	18
NECROSIS FOCAL		1	1
METAMORPHOSIS FATTY		7	6
HEPATOCYTOMEGALY	5	4	12
ANGIECTASIS	1	4	4
LIVER/CENTRILOBULAR			1
NECROSIS FOCAL			1
BILE DUCT	3	12	3
DILATATION		3	
INFLAMMATION	1	5	2
HYPERPLASIA	3	7	2
PANCREAS		5	
INFLAMMATION CHRONIC		1	
FIBROSIS		4	
PERIARTERITIS		1	
PANCREATIC ACINUS		4	
ATROPHY		4	
ESOPHAGUS			2
DILATATION			2
STOMACH		3	
ULCER FOCAL		2	
INFLAMMATION ACUTE SUPPURATIVE		1	
GASTRIC MUSCULARIS			1
HYPERPLASIA			1

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
SMALL INTESTINE		1	
ULCER FOCAL		1	
COLON		1	
ULCER FOCAL		1	
URINARY SYSTEM	7 (70%)	30 (64%)	20 (43%)
KIDNEY	6	26	16
INFLAMMATION CHRONIC	6	26	16
KIDNEY/MEDULLA			1
CONGESTION			1
KIDNEY/PELVIS	2	11	9
CALCULUS	1	7	2
INFLAMMATION SUPPURATIVE		1	2
INFLAMMATION CHRONIC		1	1
HYPERPLASIA EPITHELIAL	2	9	8
URINARY BLADDER	1	2	3
INFLAMMATION DIFFUSE			1
INFLAMMATION CHRONIC			1
HYPERPLASIA EPITHELIAL	1	2	2
U. BLADDER/MUCOSA			1
HEMORRHAGE			1
ENDOCRINE SYSTEM	7 (70%)	33 (70%)	22 (47%)
PITUITARY		3	3
HYPERPLASIA CHROMOPHOBE-CELL		3	3
ADRENAL		6	1
ATROPHY		1	
ANGIECTASIS		5	1

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ADRENAL CORTEX	1	11	8
CYTOMEGALY	1	10	6
HYPERPLASIA FOCAL			2
ANGIECTASIS		2	1
THYROID	6	24	15
ULTIMOBRANCHIAL CYST	1	2	1
CYSTIC FOLLICLES		1	
HYPERPLASIA C-CELL	5	22	14
HYPERPLASIA FOLLICULAR-CELL		1	
PARATHYROID			1
HYPERPLASIA			1
PANCREATIC ISLETS	1		1
HYPERPLASIA	1		1
HEMATOPOIETIC SYSTEM	3 (30%)	4 (9%)	6 (13%)
SPLEEN	3	4	6
FIBROSIS	1	1	
HEMOSIDEROSIS	2	1	1
ATROPHY		1	
LYMPHOID HYPERPLASIA		1	
HEMATOPOIESIS		2	5
LYMPH NODE			1
LYMPHOID HYPERPLASIA			1
REPRODUCTIVE SYSTEM		4 (9%)	10 (21%)
MAMMARY GLAND			4
HYPERPLASIA			3
HYPERPLASIA FOCAL			1
TESTIS		1	
ATROPHY		1	

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
UTERUS		1	
HEMORRHAGE		1	
UTERUS/ENDOMETRIUM		3	6
INFLAMMATION SUPPURATIVE		1	1
HYPERPLASIA			1
HYPERPLASIA CYSTIC		2	3
METAPLASIA SQUAMOUS		2	3
NERVOUS SYSTEM			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			2 (4%)
EYE/CORNEA			1
INFLAMMATION CHRONIC			1
EYE/CILIARY BODY			1
FIBROSIS			1
EYE/CRYSTALLINE LENS			1
DEGENERATION			1
EYE/CONJUNCTIVA			1
INFLAMMATION CHRONIC			1
EYE/LACRIMAL GLAND			1
INFLAMMATION CHRONIC			1
EYE/LACRIMAL DUCT			1
METAPLASIA SQUAMOUS			1

TABLE C2 FEMALE RATS: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
ALL OTHER SYSTEMS		1 (2%)	
MULTIPLE ORGANS		1	
PERIARTERITIS		1	
NO LESION REPORTED			4
AUTOLYSIS/NECROPSY PERF/NO HISTO			2
AUTOLYSIS/NO NECROPSY PERFORMED		3	3
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*		5	13
MORIBUND SACRIFICE	1	9	12
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	9	36	25

*INCLUDES AUTOLYZED ANIMALS

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

APPENDIX D

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN MICE FED DIMETHOATE IN THE DIET

TABLE D1

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN MALE MICE FED DIMETHOATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	7	50	50
ANIMALS NECROPSIED	7 (100%)	50 (100%)	50 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	7	50	50
ANIMALS WITH TUMORS	6 (86%)	11 (22%)	11 (22%)
INTEGUMENTARY SYSTEM*		3 (6%)	1 (2%)
SKIN		3	1
ULCER FOCAL		1	1
INFLAMMATION NECROTIZING		1	
HYPERPLASIA EPITHELIAL		1	
ACANTHOSIS		1	
RESPIRATORY SYSTEM		3 (6%)	1 (2%)
LUNG		3	1
EMPHYSEMA			1
INFLAMMATION FOCAL			1
INFLAMMATION FOCAL CHRONIC		2	
HYPERPLASIA ALVEOLAR-CELL		1	
CIRCULATORY SYSTEM	1 (14%)		
MYOCARDIUM	1		
MINERALIZATION	1		
DIGESTIVE SYSTEM	1 (14%)	8 (16%)	8 (16%)
LIVER		6	7
INFLAMMATION CHRONIC			1
NECROSIS FOCAL			1
CYTOPLASMIC VACUOLIZATION		1	1
HEPATOCYTOMEGALY		2	1
HYPERPLASIA NODULAR		3	4
NODULAR HYPERPLASIA			1

TABLE D1 MALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
BILE DUCT			1
INFLAMMATION CHRONIC			1
PANCREAS		1	
INFLAMMATION FOCAL CHRONIC		1	
PANCREATIC DUCT	1		
CYST	1		
PANCREATIC ACINUS		1	1
ATROPHY		1	
ATROPHY FOCAL			1
LARGE INTESTINE	1		1
NEMATODIASIS	1		1
URINARY SYSTEM			
NONE			
ENDOCRINE SYSTEM	3 (43%)	36 (72%)	39 (78%)
ADRENAL CORTEX	3	35	38
HYPERPLASIA	3	35	38
THYROID		3	1
HYPERPLASIA FOLLICULAR-CELL		2	1
CYSTIC FOLLICLES		1	
HEMATOPOIETIC SYSTEM	1 (14%)	2 (4%)	2 (4%)
SPLEEN	1	2	1
LYMPHOID HYPERPLASIA	1	1	1
HEMATOPOIESIS		1	
LYMPH NODE			1
ANGIECTASIS			1

TABLE D1 MALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
REPRODUCTIVE SYSTEM		3 (6%)	2 (4%)
SEMINAL VESICLE		1	
DISTENTION		1	
TESTIS		2	1
ATROPHY		2	
ATROPHY FOCAL			1
EPIDIDYMIS			1
INFLAMMATION CHRONIC			1
NERVOUS SYSTEM			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS			1 (2%)
EPICARDIUM			1
INFLAMMATION CHRONIC			1
NO LESION REPORTED	1	5	3
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	7	50	50
NATURAL DEATH*	1	3	2
MORIBUND SACRIFICE		6	2
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	6	41	46
*INCLUDES AUTOLYZED ANIMALS			

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

TABLE D2

SUMMARY OF THE INCIDENCE OF NONTUMOR PATHOLOGY IN FEMALE MICE FED DIMETHOATE IN THE DIET

	CONTROL	LOW DOSE	HIGH DOSE
ANIMALS INITIALLY IN STUDY	10	50	50
ANIMALS NECROPSIED	10 (100%)	50 (100%)	49 (100%)
ANIMALS EXAMINED HISTOPATHOLOGICALLY	10	50	49
ANIMALS WITH TUMORS	3 (30%)	15 (30%)	12 (24%)
INTEGUMENTARY SYSTEM			
NONE			
RESPIRATORY SYSTEM			
NONE			
CIRCULATORY SYSTEM *		1 (2%)	
HEART		1	
PERIARTERITIS		1	
MYOCARDIUM		1	
INFLAMMATION SUPPURATIVE		1	
DIGESTIVE SYSTEM	1 (10%)	7 (14%)	8 (16%)
LIVER	1	6	8
INFLAMMATION FOCAL		1	
LYMPHOCYTIC INFLAM INFILTRATE		1	2
INFLAMMATION SUPPURATIVE		1	1
GRANULOMA			1
NECROSIS FOCAL			1
HEPATOCYTOMEGALY	1		4
HYPERPLASIA NODULAR		2	2
HEMATOPOIESIS		1	
SMALL INTESTINE		1	
LYMPHOID HYPERPLASIA		1	

TABLE D2 FEMALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
URINARY SYSTEM		5 (10%)	3 (6%)
KIDNEY		2	
HYDRONEPHROSIS		1	
GLOMERULOSCLEROSIS		1	
KIDNEY/CORTEX		3	3
LYMPHOCYTIC INFLAM INFILTRATE		3	3
ENDOCRINE SYSTEM		1 (2%)	1 (2%)
THYROID		1	1
PERIARTERITIS		1	
HYPERPLASIA FOLLICULAR-CELL			1
HEMATOPOIETIC SYSTEM		7 (14%)	3 (6%)
SPLEEN		4	2
LYMPHOID HYPERPLASIA		2	
HEMATOPOIESIS		2	2
LYMPH NODE		2	2
CYST		2	
INFLAMMATION GRANULOMATOUS			1
AMYLOIDOSIS			1
CERVICAL LYMPH NODE		1	
CYST		1	
REPRODUCTIVE SYSTEM	9 (90%)	43 (86%)	39 (80%)
UTERUS/ENDOMETRIUM	9	42	35
CYST	7	29	26
INFLAMMATION		2	
INFLAMMATION SUPPURATIVE	2	3	
HYPERPLASIA		3	1
HYPERPLASIA CYSTIC		7	8

TABLE D2 FEMALE MICE: NONTUMOR PATHOLOGY (CONT.)

	CONTROL	LOW DOSE	HIGH DOSE
OVARY	3	5	2
FOLLICULAR CYST		3	1
INFLAMMATION		2	
INFLAMMATION SUPPURATIVE	3	1	1
OVARY/SEROSA		3	6
CYST		2	6
MULTIPLE CYSTS		1	
NERVOUS SYSTEM			
NONE			
MUSCULOSKELETAL SYSTEM			
NONE			
SPECIAL SENSE ORGANS			
NONE			
ALL OTHER SYSTEMS			
NONE			
NO LESION REPORTED		4	7
AUTOLYSIS/NO NECROPSY PERFORMED			1
ANIMAL DISPOSITION SUMMARY			
ANIMALS INITIALLY IN STUDY	10	50	50
NATURAL DEATH*	1	1	2
MORIBUND SACRIFICE	2	4	3
SCHEDULED SACRIFICE			
ACCIDENTALLY KILLED			
TERMINAL SACRIFICE	7	45	45

*INCLUDES AUTOLYZED ANIMALS

* SYSTEM PERCENTAGES ARE BASED ON NUMBER OF ANIMALS NECROPSIED.

☆ U. S. GOVERNMENT PRINTING OFFICE : 1977 241-161/3009

DHEW Publication No. (NIH) 77-804